REMARKS

Amended and New Claims

Claim 1 has been amended to replace the term "comprising" with the term "consisting essentially of". New Claims 38 through 52 have been added. No new matter has been added and support for the new and amended claims is provided in the original claims and throughout the specification. *See* page 12, paragraphs [0041] and [0042] and page 15, paragraph [0070] for examples.

Claims 1, 4-6, 8, 10-13, 17 and 19 are not anticipated by U.S. Pat. No. 6,693,129

Claims 1, 4-6, 8, 10-13, 17 and 19 have been rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rath (U.S. Pat. No. 6,693,129). Rath discloses compositions and methods for lowering plasma lipoprotein levels in humans.

The pending claims are anticipated by the prior art "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". M.P.E.P. §2131. Additionally, in order to establish a *prima facie* case of obviousness, three basic criteria must be met. M.P.E.P. §2142. First, the prior art must suggest the desirability of the claimed invention. Second, the prior art must create a reasonable expectation of success in the practice of the invention under consideration. Third, all limitations of the claims of the present application must be taught or suggested. If the prior art fails to meet one or more of these criteria, a *prima facie* case of obviousness cannot be asserted.

Claim 1 has been amended to replace the transitional phrase "comprising" with "consisting essentially of". The claim now recites a method for treating dyslipidemia *consisting essentially of* administering to an individual in need thereof an effective dose of a chromium complex and biotin. The transitional phrase "consisting essentially of" limits the scope of the claim to the specificed materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. M.P.E.P. §2111.03. In the present claims, the amendment to Claim 1 limits the method of the claim to the administration of a chromium complex, biotin and any other compounds that do not materially affect the effects of chromium and biotin administration on blood lipid levels. Compounds that materially affect blood lipid

levels are excluded from the methods of Claims 1, 4-6, 8, 10-13, 17 and 19 by the use of the transitional phrase "consisting essentially of".

The compositions disclosed and claimed by Rath in the '129 patent contain at least 38 ingredients, all of which are disclosed to affect blood lipid levels. All of the 38 ingredients or ingredient types are required for inclusion in the '129 compositions. As detailed above, the present claims are limited to chromium, biotin and any compound that does not materially affect blood lipid levels. As the Rath patent does not suggest or discuss the use of a composition consisting essentially of a chromium complex and biotin for the treatment of dyslipidemia and does not suggest or disclose the effects of concurrent chromium and biotin administration in the absence of other ingredients that affect serum lipid levels, the Rath patent does not expressly or inherently describe each and every limit of the amended claims. Therefore the prior art does not anticipate the present claims. The prior art does not suggest the desirability of a composition consisting essentially of a chromium complex and biotin. It does not create a reasonable expectation of success for the use of a chromium complex and biotin composition without the simultaneous inclusion of a myriad of other active ingredients. It does not teach or suggest a composition consisting essentially of a chromium complex and biotin, wherein all the other ingredients specified for the claimed composition are not present. Thus the prior art fails to meet any of the three basic criteria for a *prima facie* case of obviousness for the pending claims.

The prior art fails to create anticipation and obviousness for newly amended Claim 1 and dependent Claims 4-6, 8, 10-13, 17 and 19. Applicants respectfully request withdrawal of the rejection of these Claims under 35 U.S.C. §102(b) as anticipated by or under 35 U.S.C. 103(a) as obvious over Rath (U.S. Pat. No. 6,693,129).

Claims 1-20 and 23-27 are not obvious in view of the prior art

Claims 1-20 and 23-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over McCarty (U.S. Pat. No. 5,789,401) or McCarty (U.S. Pat. No. 5,929,066) in view of De La Harpe (U.S. Pat. No. 5,948,772), Jensen (U.S. Pat. No. 5,194,615) and Brand-Miller (*Am. J. Clin. Nutr.* 59(suppl):747S-752S, 1994) in the previous Office Action. The rejection of the claims is maintained in the present Office Action, in view of the same prior art and in further view of the Rath patent discussed above ('129).

In order to establish a prima facie case of obviousness, three basic criteria must be met. M.P.E.P. §2142. First, the prior art must suggest the desirability of the claimed invention. Second, the prior art must create a reasonable expectation of success in the practice of the invention under consideration. Third, all limitations of the claims of the present application must be taught or suggested. If the prior art fails to meet one or more of these criteria, a *prima facie* case of obviousness cannot be asserted.

The PTO asserts that, in their responses to previous Office Actions, the Applicants have argued against nonobviousness improperly by attacking each reference individually. The PTO states in the present Office Action that:

> "[T]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the reference would have suggested to those of ordinary skill in the art." Page 4 of Paper 20040115

In combining the prior art references, the PTO has improperly built a case for rejection of the present claims based on inferences that are in no way supported by the prior art. In the present Office Action, the PTO declares that the De La Harpe patent ('772) clearly discloses that hypercholesterolemia is present in diabetes. The PTO then states that since diabetics suffer from ineffective insulin and compromised glucose metabolism and since hypercholesterolemia is present in diabetics, that one with skill in the art would expect that by administering biotin, a substance "known to make insulin more effective" according to the PTO, hypercholesterolemia can be treated. The PTO concludes by stating that:

> "Further, there is no requirement that the prior art treat all forms of dyslipidemia as long as it would be expected to be effective in treating hypercholesterolemia *which results from ineffective insulin and compromised glucose metabolism* the prior art reads on the claimed invention." Page 4 of Paper 20040115 (emphasis added)

From the disclosure of the prior art, the PTO has concluded that since diabetics suffer from ineffective insulin and compromised glucose metabolism and that hypercholesterolemia is often present in diabetics, it follows that the ineffective insulin and compromised glucose metabolism are the cause of hypercholesterolemia in diabetics and that by treating ineffective insulin and compromised glucose metabolism, hypercholesterolemia will also be treated. However, factual support for such conclusions does not exist in the prior art references. The coincidence of multiple symptoms or syndromes indicative of disease in a patient population is not evidence of a causal relationship between those symptoms or syndromes. The symptoms or syndromes may be unrelated or they may each be an effect of an additional condition.

In the De La Harpe patent ('772), a range of effects created in normal laboratory animals upon depletion of dietary chromium are described. Later, a list of disease syndromes that characterize "in large part" diabetes mellitus are listed and a causative link between hypercholesterolemia and coronary disease is disclosed. Additionally, a number of positive effects which arise from chromium supplementation are described in '772. In the disclosure of the McCarty patents ('401 and '066), studies done on the effects of biotin supplementation are described. These patents disclose that biotin supplementation increases oral glucose tolerance in diabetic mice, reduces fasting blood glucose levels in patients with Type I diabetes who have temporarily discontinued insulin injections, and improve pancreatic beta cell function in patients with Type II diabetes.

In the 2nd paragraph of Page 4 of the Office Action, the PTO states the reasoning that underlies the rejection based on the combined disclosure of the prior art. As noted above, the PTO has concluded that: 1) the treatment of insulin ineffectiveness and compromised glucose metabolism would effect a lowering of cholesterol levels; and 2) that biotin is known to be effective in making insulin more effective. However, the disclosures of the prior art references, either taken individually or collectively, do not support or suggest either of the PTO's conclusions. None of the references, alone or combined, suggest a causal relationship in which hypercholesterolemia is a consequence of ineffective insulin and compromised glucose metabolism. There is also no disclosure or suggestion in the references as to a mechanism by which biotin affects glucose tolerance. According to the PTO, it is known from the disclosures of the prior art that biotin acts by making insulin more effective However, the McCarty patents state that biotin administration lowered fasting plasma glucose levels in Type I diabetics who had

temporarily discontinued their insulin injections. Type I diabetes is characterized by a lack of endogenous insulin production due to the destruction of the pancreatic beta cells that produce insulin. Type I diabetics who discontinue their insulin injections would have negligible amounts of insulin in their bodies. Yet biotin supplementation lowers serum blood glucose levels significantly in Type I diabetics that are not receiving insulin injections. Therefore, the prior art provides evidence that the activity of biotin is actually due to a mechanism independent of the function of insulin and is not due to an increase in the effectiveness of insulin.

The PTO states that the rejection is based on a combination of references and that there is no requirement that the claimed invention must be expressly suggested in any one or all of the references. However, somewhere in the combined disclosure of the references, there must be disclosure or suggestion for each idea linking the methods of the present claims to their intended purposes, with a reasonable expectation of success. As discussed above, there is no support in the prior art for the PTO's inference that a treatment for ineffective insulin and compromised glucose metabolism would subsequently provide a treatment for hypercholesterolemia in diabetes as well. No mechanism for the activity of biotin is suggested, disclosed or supported by the combined disclosure of the prior art. The PTO states that it is known that biotin makes insulin more effective, when the disclosure of the prior art references makes no such claim and actually teaches away from the PTO's conclusion.

Any evidence or suggestion of the effectiveness of biotin in altering serum lipid levels in any circumstance or as part of any composition is found exclusively in the disclosure of the present application. Any judgment on obviousness must only be based on knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made. This does not include knowledge gleaned from the applicant's disclosure. As there is no suggestion that biotin supplementation would affect lipid levels in any way in the cited prior art, the use of biotin to affect lipid levels is not obvious.

The PTO has cited an additional piece of prior art in the pending Office Action, the Rath patent ('129). As detailed above, Claim 1 has been amended to exclude the compositions of Rath. The disclosure of the '129 patent does not meet the three basic criteria for a *prima facie* case of obviousness for the amended claim or its dependents. The '129 patent does not suggest that a composition consisting essentially of a chromium complex and biotin and lacking any of the other ingredients specified by Rath would be desirable. It does not create a reasonable

expectation of success for altering serum lipid levels through the use of a composition consisting essentially of a chromium complex and biotin. The limitation of the present claims, which excludes any additional ingredient that may affect serum lipid levels from the compositions of a chromium complex and biotin, is not taught in the '129 patent. Thus, the '129 patent fails to provide any of the required criteria for the establishment of a *prima facie* case of obviousness.

With regard to the three basic criteria for obviousness, the combined disclosure of the prior art does not establish obviousness. There is no suggestion or motivation to use biotin in the treatment of dyslipidemia or that biotin and chromium would be synergistically effective in the treatment of dyslipidemia. The combined disclosure of the prior art does not provide a reasonable expectation that the administration of a synergistic amount of a chromium complex and biotin would have an effect on serum lipid levels. The combined disclosure of the prior art references does not teach or suggest the administration of a composition consisting essentially of a chromium complex and biotin for the treatment of dyslipidemia. As the combined disclosure of the prior art references fails to meet any of the criteria for a *prima facie* case of obviousness, Applicants respectfully request the withdrawal of the rejection of Claims 1-20 and 23-27 under 35 U.S.C. §103(a) as being unpatentable in view of the cited prior art.

The synergistic effects of chromium and biotin on serum lipid levels is unexpected

In the response to the previous Office Action, Applicants amended the claims to limit the compositions to synergistic amounts of a chromium complex and biotin. The PTO states in the pending Office Action that the evidence of synergy is not commensurate in scope with the breadth of the claims because "only specific amounts are tested and only glucose uptake and HDL-change are shown". The PTO further states that the McCarty patents disclose the synergistic effects of adminstering a composition of chromium and biotin, thus any synergy seen in the administration of chromium and biotin would be expected. Applicants respectfully disagree.

Figures 2 and 14 present evidence of the synergy of chromium and biotin on changes in HDL levels and glucose uptake. In each experiment, a variety of chromium and biotin amounts are administered alone or in combination. The figures show that the administration of a composition of chromium and biotin together has a greater than additive effect on glucose uptake and on changes in HDL levels in laboratory rats.

The PTO states that the evidence of synergy is not commensurate with the breadth of the scope of the claims because only specific amounts are tested and only glucose uptake and HDL change are shown. However, the specific amounts tested are sufficient to show the synergistic effects. One with skill in the art would expect to see synergistic effects with the administration of other amounts of chromium and biotin found in the ranges given in the claims. Additionally, one with skill in the art would appreciate that the absolute levels of various blood lipids is not as important as the ratios between the concentrations of the lipids when evaluating a patient's risk for disease due to dyslipidemia. Hence, a rise in HDL levels would indicate reduced risk for disease and would be evidence of a healthier blood lipid profile independent of the levels of other blood lipids.

The PTO has claimed that the synergy between chromium and biotin in the disclosures of McCarty means that the synergy of chromium and biotin on serum lipid levels would be expected by one with skill in the art. However, as explained above, the combined disclosure of the prior art does not suggest, disclose or support any effects of biotin on serum lipid levels or the use of biotin for the treatment of dyslipidemia, alone or in combination with another compound. Hence, any effects of biotin, alone or in combination with another compound, would be unexpected, including the synergistic effects demonstrated in Figure 14.

The prior art collectively contains no support or suggestion of a role for biotin in the treatment of dyslipidemia and does not disclose, suggest or teach that a composition of chromium and biotin administered together would have any effects on serum lipid profiles beyond those seen with the administration of chromium by itself, let alone *synergistic* effects on changes in HDL levels. Hence, the combined disclosure of the prior art fails to meet any of the criteria for a *prima facie* case for obviousness.

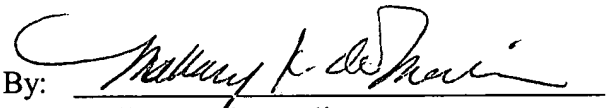
CONCLUSION

Based on the arguments above, Applicants request the removal of all claim rejections and assert the application is ready for allowance. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 7/23/04

By: 

Mallary K. de Merlier
Registration No. 51,609
Attorney of Record
Customer No. 20,995
(619) 235-8550

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